

Online Research @ Cardiff

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <https://orca.cardiff.ac.uk/id/eprint/114415/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Bhattacharya, Sohinee and Bhattacharya, Siladitya ORCID:
<https://orcid.org/0000-0002-4588-356X> 2016. How dangerous is weight gain between pregnancies? Nature Reviews Endocrinology 12 (3) , pp. 128-103. 10.1038/nrendo.2016.4 file

Publishers page: <http://dx.doi.org/10.1038/nrendo.2016.4>
<<http://dx.doi.org/10.1038/nrendo.2016.4>>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies.

See

<http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



Strapline: Obesity

Title: How dangerous is weight gain between pregnancies?

Sohinee Bhattacharya and Siladitya Bhattacharya

Standfirst:

Babies of women with a high body mass index (BMI) have a higher chance of dying in utero or soon after birth, but it is unclear how weight gain between pregnancies affects this phenomenon. A new study suggests that a BMI rise of ≥ 4 kg/m² between pregnancies can amplify the risk of stillbirth and neonatal mortality.

Refers to Cnattingius, S. & Villamore, E. Weight change between successive pregnancies and risks of stillbirth and infant mortality: a nationwide cohort study. *Lancet* [http://dx.doi.org/10.1016/S0140-6736\(15\)00990-3](http://dx.doi.org/10.1016/S0140-6736(15)00990-3) (2015)

Overweight and obesity in early pregnancy are associated with adverse health outcomes for both mother and baby^{1,2}. However, weight loss interventions during pregnancy itself have not been shown to be effective at reducing stillbirths and infant mortality³. Although weight reduction before pregnancy should be effective, robust clinical evidence for this is lacking. In a recent paper, Cnattingius and Villamore⁴ used population-based data from Sweden to assess the effect of maternal weight change between pregnancies on the risk of subsequent stillbirth and infant mortality. They found that the risk of stillbirth increased by 55% and infant mortality by 29% in mothers with an increase in BMI of ≥ 4 kg/m² between the first and second pregnancies compared with mothers who had a stable weight between pregnancies. In overweight women weight loss before the next pregnancy was associated with a reduction in risk of neonatal mortality but not stillbirth.

Improvements in maternal and perinatal health care have meant that stillbirth has become a rare occurrence in developed countries. Yet, a study published in 2011 on time trends in stillbirth rates across 35 European countries indicated that further reductions are possible⁵. Maternal overweight and obesity was the foremost modifiable risk factor in a systematic review and meta-analysis of risk factors for stillbirth in high-income countries, contributing 8–18% population attributable risk⁶. Advanced maternal age⁷ also has a major influence on adverse pregnancy outcomes, with age >35 years associated with a population attributable risk of 7–11%. Thus, deferring the next conception after losing a baby might not necessarily make a subsequent pregnancy safer for the baby if this delay leads to a significant increase in maternal age. Maternal smoking⁸ is believed to be an additional risk factor and smoking cessation programmes in pregnancy have been shown to be effective in reducing the prevalence of stillbirth⁸.

In the current paper, Cnattingius and Villamore⁴ identified high BMI in the first pregnancy, smoking in both pregnancies and long inter-pregnancy intervals as potential negative influences on perinatal mortality. Surprisingly, the effect of advanced maternal age in their paper was less pronounced compared with previously reported analyses based on the same Swedish register⁷. In interpreting the latest findings, it is worth acknowledging that the magnitude of the risk associated with increased BMI for women in their second pregnancy is not dissimilar to that faced by all women giving birth for the first time. Among women who have been pregnant before, those who have had a previous pregnancy loss are at a higher risk of a similar event⁹. As Cnattingius and Villamore excluded women who had a miscarriage or stillbirth in their first pregnancy from their analysis, they were unable to explore the effect of weight loss in preventing recurrence of pregnancy loss.

A BMI increase of $\geq 4 \text{ kg/m}^2$ between pregnancies can push a woman with normal weight or overweight into the overweight or obese category, respectively, in her next pregnancy. So is the observed effect due to the increase in BMI or the high BMI itself? The authors explored this question by investigating the effect of BMI change on perinatal and infant mortality in two groups of women; those with BMI $\geq 25 \text{ kg/m}^2$ and those with a BMI $< 25 \text{ kg/m}^2$ in their first pregnancy. This analysis showed that in women with a normal BMI (but not those who were overweight or obese), weight gain increased the risk of stillbirth, neonatal mortality and infant mortality. This probably indicates that BMI per se, rather than weight gain, is responsible for the adverse outcome.

On the basis of their findings, the authors recommend that normal weight women should be advised not to gain weight between pregnancies and women with overweight or obesity should be counselled to lose weight before the next pregnancy. Achieving and maintaining a healthy weight has many benefits for both the mother and the child; however, the practical implications of this recommendation might not be simple. Most women report a modest gain in weight between pregnancies but as long as this does not lead to a rise in BMI of more than $1\text{--}2 \text{ kg/m}^2$, risks during subsequent pregnancies should not be increased. Weight loss in women with overweight or obesity might reduce risks in the next pregnancy, but no effective interventions currently exist that can achieve weight loss quickly such that the benefits of weight loss are not offset by advanced maternal age. Researchers tend to conduct and present their obesity-related research findings in terms of BMI expressed as weight in kg divided by (height in m)² and the current article is no exception. We feel that this measure is of limited value to women and their clinicians who are more used to thinking in terms of absolute weights.

Although the relative risk of stillbirth associated with weight gain between pregnancies seems to be large (55%) when compared with weight-stable women, the increase in absolute risk remains low (1.5

per 1,000 births for ≥ 4 kg/m² increase in BMI). These absolute values are even lower for infant mortality (0.9 per 1,000 births) and neonatal mortality (0.5 per 1,000 births). This low risk is attributable to the fact that stillbirths and neonatal and infant deaths are rare in the general population in developed countries, so a large number of women would need to gain a substantial amount of weight between pregnancies to increase the risk of these adverse events. For example, 11,111 women would need to gain ≥ 4 kg/m² in BMI to cause one extra neonatal death.

In an ideal world, we would assess the effects of weight management interventions on perinatal and infant mortality using randomised controlled trials. However, for rare outcomes such as stillbirths and infant deaths, analysis of large population-based databases offers a practical alternative to randomized controlled trials. Nevertheless, the findings from these analyses should be interpreted with caution. The finding of an association (in this case between weight change and perinatal and infant mortality) does not necessarily imply causation. The biological mechanism to explain how weight gain affects perinatal or infant mortality remains elusive. One theory suggests that fat deposition triggers an inflammatory pathway that results in maternal conditions in pregnancy such as high blood pressure (preeclampsia), diabetes mellitus and intrauterine fetal growth restriction, which are associated with perinatal deaths¹⁰. Infant mortality is probably more likely to be influenced by social and environmental factors after birth, which could also contribute to maternal weight gain.

Women should be encouraged to achieve a healthy prepregnancy weight; however, modest weight gain between successive pregnancies has limited impact on perinatal and infant mortality

Sohinee Bhattacharya and Siladitya Bhattacharya are at the Institute of Applied Health Sciences School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen AB25 2ZL, UK.

Correspondence to Siladitya Bhattacharya s.bhattacharya@abdn.ac.uk

1. Cnattingius, S., Bergström, R., Lipworth, L. & Kramer, M. S. Prepregnancy weight and the risk of adverse pregnancy outcomes. *N. Engl. J. Med.* 338, 147-152 (1998).
2. Chu, S. Y. et al. Maternal obesity and risk of stillbirth: a meta-analysis. *Am. J. Obstet. Gynecol.* 197, 223-228 (2007).
3. Muktabhant B, Lawrie TA, Lumbiganon P, Laopaiboon M. Diet or exercise, or both, for preventing excessive weight gain in pregnancy. *Cochrane Database of Systematic Reviews* 2015, Issue 6. Art. No.: CD007145. DOI: 10.1002/14651858.CD007145.pub3

4. Cnattingius, S. & Villamore, E. Weight change between successive pregnancies and risks of stillbirth and infant mortality: a nationwide cohort study. *Lancet* [http://dx.doi.org/10.1016/S0140-6736\(15\)00990-3](http://dx.doi.org/10.1016/S0140-6736(15)00990-3) (2015).
5. Cousens, S. et al. National, regional, and worldwide estimates of stillbirth rates in 2009 with trends since 1995: a systematic analysis. *Lancet* 377, 1319-30 (2011).
6. Flenady, V. et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. *Lancet* 377, 1331-1340 (2011).
7. Nybo-Andersen, A. M., Wohlfahrt, J., Christens, P., Olsen, J. & Melbye, M. Maternal age and fetal loss: population based register linkage study. *BMJ* 320, 1708-1712 (2000).
8. Lumley J, Chamberlain C, Dowswell T, Oliver S, Oakley L, Watson L. Interventions for promoting smoking cessation during pregnancy. *Cochrane Database of Systematic Reviews*, Issue 3. Art. No.: CD001055. <http://dx.doi.org/10.1002/14651858.CD001055.pub3>.
9. Regan, L., Braude, P. R. & Trembath, P. L. Influence of past reproductive performance on risk of spontaneous abortion. *BMJ* 299, 541-545 (1989).
10. Villamor, E. & Cnattingius, S. Interpregnancy weight change and risk of adverse pregnancy outcomes: a population-based study. *Lancet* 368, 1164-70 (2006).

Competing interests statement

The authors declare no competing interests.

Author biographies

Sohinee Bhattacharya, MBBS, PhD is Senior Lecturer in Obstetric Epidemiology at the Institute of Applied Health Sciences, University of Aberdeen. She is interested in using routinely collected data for epidemiological research and is responsible for managing the Aberdeen Maternity and Neonatal Databank, an obstetric database going back to 1950.

Prof. Siladitya Bhattacharya MBBS, MD, FRCOG is Professor of Reproductive Medicine, University of Aberdeen and Director of the Institute of Applied Health Sciences, School of Medicine and Dentistry, University of Aberdeen

His main research interests include reproductive epidemiology and randomised clinical trials of interventions in reproductive health care.

Box 1. Definitions of stillbirth and infant mortality used in the article by Cnattingius and Villamore

Stillbirth: Delivery of a dead baby at or after 28 weeks of gestation

Neonatal mortality: Death of a baby within the first 28 days of delivery
Post Neonatal mortality: Death of a baby after the first 28 days but within the first year of delivery
Infant mortality: Death of a baby within the first year of life and includes both neonatal and post neonatal mortality.